REMARKS

I. New Claims

Applicant has now added claims 30-34 to the application. Claim 30 sets forth the list of polymers from which the polymer of claim 19 may be selected. Claim 31 is directed to a PVAP/PVP complex which further claims the spectroscopic data of the complex. Claim 32 is directed to a polymer complex formed by Applicant's process. Claim 33 is directed to a polymer-entrapped drug comprising a drug that is insoluble in organic solvent, but soluble or suspendable in an alkaline solution and insoluble in aqueous acidic solutions. Finally, claim 34 notes the spectroscopic data of the complex of claim 33.

II. Restriction Requirement

Pursuant to the Examiner's requirement, Applicant hereby elects the species consisting of acrylic and polyvinylacetate copolymers. Claims 3 and 18 have now been canceled. The polymers of new claim 30 are limited to the acrylic and polyvinylacetate copolymers.

III. Claim Rejections - 35 U.S.C. § 103

Claims 1-29 were rejected under 35 U.S.C. 103(a), as being unpatentable over Gupta et al. Drug Development and Industrial Pharmacy (1994) or M.A. Elegakey et al. P.P.S. 434-440 or Takayana Chem. Pharm. Bull. PPS. 5921-4926.

The Examiner states that "[t]he combination of polyvinylpyrrolidone and carboxylic polymer is known in the art for properties of the complexes formed by same." (Office Action, p. 3). The Examiner then argues that while PVAP-PVP complexes of Applicant's working examples would be considered to non-obvious in view of the cited prior art, "[t]he claims do not clearly define a 'complex' of PVAP/PVP, however, and may be physically equivalent to a mixture

of ingredients in which PVAP is not complexed, but is added as an auxiliary component, i.e., as a plasticizer." (Office Action, p. 3).

Applicant thanks the Examiner for providing the above information pertaining to potentially non-obvious subject matter in this application. Independent claims 1 and 8, and new independent claims 31 and 33 have now been amended to specify that the complex is PVAP/PVP. Further, Applicant has amended the body of the claims to specify that the polymer/PVP is a complex. It therefore believed that all the claims do clearly define a polymer/PVP and/or PVAP/PVP complex.

The Examiner's contention that a PVP mixture with PVAP as an additive would be obvious in view of "the known plasticizing properties of PVAP" is not accurate. (See attached Declaration of Dr. Vijay Kumar, para. 5). The inventor, Dr. Kumar, states that he is not aware of any previous reports of PVAP as a plasticizer. (Decl. V. Kumar, para. 6). In order for PVAP to serve as a plasticizer, it must be miscible with PVP, which it is not. (Decl. V. Kumar, para. 7). Further, PVAP/PVP complex dries to form a hard material, suggesting that there is no plasticization effect by either the PVAP or PVP. (Decl. V. Kumar, para. 8).

In addition, Applicant respectfully submits that the claimed invention is also non-obvious with respect to complexes formed with other polymers having at least one free carboxyl group formed in accordance with the process of the invention, as set forth in independent claims 19 and 32. It is this free carboxyl group which allows for the formation of hydrogen bonds between carbonyl groups of PVP and carboxylic groups of the other polymer at some point of the polymer chains. (See Spec., p. 13). The references of record do not teach or suggest a complex formed by the process of combining a polymer having at least one free carboxyl group and a drug in an

aqueous alkaline solution or an organic solvent to form a mixture, and adjusting the pH of the mixture to an acidic pH to form entrapped drug granules

IV. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1-29 were rejected under 35 U.S.C. § 112, second paragraph. The Examiner states that the physical structure of the "complex" as reported by spectroscopic data "is critical to the applicants' disclosed view of the invention." (Office Action p. 4). The Examiner further states that the term "complex" is "non-descriptive of the drug containing PVP/PVAP product which is disclosed as possessing required release and physical properties. Applicant respectfully traverses this rejection.

The standard for definiteness under 35 U.S.C. § 112, second paragraph is one of reasonableness under the circumstances. See e.g. Charvat v. Commissioner of Patents, 503 F.2d 138, 147-151 (D.C. Cir. 1974). The issue is whether, in the light of the teachings of the prior art and of the particular invention, the claims set out and circumscribe a particular area with a reasonable degree of precision and particularity. In re Moore, 439 F.2d 1232, 1235 (CCPA 1971).

Applicant would respectfully note that the spectroscopic data included in the application was intended to simply verify the presence of the claimed polymer and PVP, and did not intend to make it a definitive feature of the claimed complex. Further, since this spectroscopic data would inherently pertain to any polymer/PVP complex of this invention, it is not believed that it is necessary to include the data as a limitation of the claimed invention in order for the claims to have a "reasonable degree of precision and particularity" to persons skilled in the art. Applicant therefore respectfully requests that this ground of rejection be withdrawn.

In the interest of expediting prosecution, Applicant has added the spectroscopic data of the polymer/PVP complex to claims 31 and 34. Thus, at least these claims are sufficiently definite under 35 U.S.C. 112, paragraph 2.

V. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Finally, the Examiner has rejected claims 1-28 under 35 U.S.C. § 112, first paragraph on the basis that the claims are not supported for the scope of drug which can be encapsulated in the complex. Specifically, the Examiner states that while ibuprofen and other actives of similar solubility and properties are presumed to be useful, "the specification does not explain the forces between drug and complex such as bonding, etc. which would enable the use of an unlimited number of species unrelated in chemical structure to ibuprofen."

The test for enablement under § 112, first paragraph, is "whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation." Ex Parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. and Int'f 1986). In this case, the Board stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. at 547.

As a preliminary matter, Applicant would note that the claims directed to the polymer complex of polymer and PVP (claims 1-2, 4-7, and 31-32) do not include the encapsulated drug as an element. Thus, the Examiner's rejection should not apply to these claims.

With respect to the remaining claims, Applicant has now set forth that the drug "is insoluble in organic solvent, but soluble or suspendable in an alkaline solution and insoluble in aqueous acidic solutions." Support for this language is found on page 17 of the specification, where it notes that any drug meeting these solubility requirements is appropriate for encapsulation in the complex. It is respectfully submitted that the this language provides sufficient teaching to persons skilled in the art to make and use Applicant's invention without an undue amount of experimentation. Using Applicant's solubility teachings, persons skilled in the art of pharmaceutics can readily ascertain appropriate drugs for use in the invention besides those specifically enumerated.

Moreover, Applicant would respectfully submit that the Examiner's contention that the claimed drug entrapment procedure cannot be generalized for all drugs is not accurate. (Decl. V. Kumar, para. 9). Neither of the polymers in the claimed complex forms a complex with the ibuprofen. (Decl. V. Kumar, para. 10). Instead, the evidence shows that the entrapment of ibuprofen by the PVAP/PVP is a physical process. (Decl. V. Kumar, para. 8). This indicates to persons skilled in the art that all drugs that have the claimed solubility profiles are useful in the invention. (Decl. V. Kumar, para. 10).

To demonstrate that ibuprofen dues not interact with PVAP or PVP, each polymer was reacted with ibuprofen, separately, under the identical conditions described under Preparation method A on p. 20 of the specification. (Decl. V. Kumar, para. 11). The processing of ibuprofen in the presence of PVP produced a cloudy suspension, which had to be centrifuged in order to obtain the powder for analysis by the powder X-ray diffraction and infrared spectroscopic methods. The infrared spectrum of the treated sample was identical to that of the untreated sample. (Decl. V. Kumar, para. 12). The powder X-ray diffraction pattern of the treated sample

showed the same peak pattern as that of the raw ibuprofen, but the peaks were weaker in intensity. (Decl. V. Kumar, para. 12). PVP is highly water-soluble and, hence, remained in solution. (Decl. V. Kumar, para. 12).

The processing of ibuprofen in the presence of PVAP resulted in an immediate precipitation of a fine powder, which was characterized by infrared spectroscopy to be a mixture of PVAP and ibuprofen. (Decl. V. Kumar, para. 13). This was not surprising because PVAP, owing to the presence of the carboxylic group, is known to precipitate in low pH acid solutions. (Decl. V. Kumar, para. 13). The infrared spectra of the powdered sample collected and that of the raw ibuprofen are shown in FIG. 3 attached to Dr. Kumar's declaration. (Decl. V. Kumar, para. 13). The powder X-ray diffractogram of the powdered sample showed the same peak pattern as was observed for the other samples of ibuprofen (i.e., raw and treated ibuprofen), except for that the peaks were much broader and weaker in intensity. (Decl. V. Kumar, para. 14). In my opinion, the broadening and reduced intensity of peaks are due to both partial amorphinization of ibuprofen during processing and the presence of PVAP, an amorphous material as an impurity in the sample. (Decl. V. Kumar, para. 15).

Interestingly, the PVAP-ibuprofen coprecipitate readily and completely dissolved in 95% aqueous ethanol. (Decl. V. Kumar, para. 16). In contrast, the PVAP/PVP complex entrapped granules of ibuprofen, when suspended in the same solvent, allowed the dissolution of ibuprofen only. (Decl. V. Kumar, para. 16). The PVAP/PVP complex remained insoluble. (Decl. V. Kumar, para. 16). Further, the coprecipitate exhibited a bitter taste, whereas the granules were palatable. (Decl. V. Kumar, para. 16). The results of this study indicate that: (a) PVAP alone cannot entrap ibuprofen; and (b) the coprecipitate is a physical mixture of PVAP and PVP, not a complex. (Decl. V. Kumar, para. 17).

For all of these reasons, it is believed the claims comply with the requirements of Section 112, first paragraph.

VI. Allowable Subject Matter

The Examiner notes that PVAP-PVP complexes of the working examples of the application are considered to be unobvious from the cited Prior Art information. Applicant has attempted to redraft claims 1-2, 4-9, 11-14, 16 accordingly such that it is believed at least these claims are in allowable form. Further, it is believed that at least new claims 31, 33, and 34 are also in allowable form.

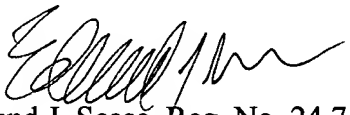
VII. Conclusion

For the above-stated reasons, Applicants respectfully request allowance of the application. If the Examiner believes it would assist in the prosecution, Applicant would encourage the Examiner to telephone the attorney-of-record at 515-288-3667.

Enclosed is the fee of $117 for the addition of three new independent claims. If this fee is incorrect, please consider this a request to credit or debit Deposit Account No. 26-0084 accordingly.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



Edmund J. Sease, Reg. No. 24,741
ZARLEY, MCKEE, THOMTE, VOORHEES
& SEASE
Attorneys of Record

801 Grand Ave., Suite 3200
Des Moines, Iowa 50309-2721
515-288-3667 -wm-

AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE — DO NOT FILE

In the Claims

Claims 1, 8, and 19 have been amended as follows:

1. (Amended)

A polymer complex for entrapping drug granules comprising:

a complex of polyvinyl acetate phthlate (PVAP) [polymer having at least one free carboxyl group]; and

polyvinylpyrrolidine (PVP).

Claim 3 has been canceled.

8. (Amended)

A polymer-entrapped drug comprising:

a drug that is insoluble in organic solvent, but soluble or suspendable in an alkaline solution and insoluble in aqueous acidic solutions;

a complex of polyvinyl acetate phthlate (PVAP) [polymer having at least one carboxyl group]; and

polyvinylpyrrolidone (PVP);

said drug being entrapped in the PVAP-PVP complex.

Claims 10, 15, 17, and 18 have been canceled.

19. (Amended)

A method of making a polymer entrapped drug comprising the steps of:

combining [a] at least one polymer having at least one free carboxyl group and a drug in [a non-acidic medium] an aqueous alkaline solution or an organic solvent to form a mixture, said drug being insoluble in organic solvent, but soluble or suspendable in an alkaline solution and insoluble in aqueous acidic solutions; and

adjusting the pH of the mixture to an acidic pH to form entrapped drug granules.

Claim 20 has been canceled.

Claims 30-34 have been added.

30. (New)

A method according to claim 19 wherein the polymer is selected from the group consisting of acrylic polymers, acrylic copolymers, methacrylic acid polymer, methacrylic acid copolymers, and polyvinyl acetate phthlate (PVAP).

31. (New)

A polymer complex for entrapping drug granules comprising:

a complex of polyvinyl acetate phthlate (PVAP); and

polyvinylpyrrolidine (PVP);

said PVAP-PVP complex having bands at about 1657 cm^{-1} and 1724 cm^{-1} in the spectrum of the PVAP-PVP complex.

32. (New)

A polymer complex for entrapping drug granules formed by the process of:

combining at least one polymer having at least one carboxyl group and a drug in an aqueous alkaline solution or an organic solvent to form a mixture, said drug being insoluble in organic solvent, but soluble or suspendable in alkaline solutions and insoluble in aqueous acidic solutions; and

adjusting the pH of the mixture to an acidic pH to form entrapped drug granules.

33. (New)

A polymer-entrapped drug comprising:

a drug that is insoluble in organic solvent, but soluble or suspendable in an alkaline solution and insoluble in aqueous acidic solutions;

said drug being entrapped in a complex of polyvinyl acetate phthlate (PVAP) and polyvinylpyrrolidine (PVP).

34. (New)

A polymer-entrapped drug according to claim 33 wherein the PVAP-PVP complex has bands at about 1657 cm^{-1} and 1724 cm^{-1} in the spectrum of the PVAP-PVP complex.